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## Similar effects of rofecoxib and indomethacin on the incidence of heterotopic ossification after hip arthroplasty

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**Background** Although indomethacin is effective in preventing heterotopic ossification (HO) after primary total hip arthroplasty, side effects are frequently observed. In the last decade a new class of drugs—the COX-2 selective nonsteroidal anti-inflammatory drugs—has been developed. To investigate the effect of these COX-2 selective NSAIDs on heterotopic ossification (HO) after primary total hip arthroplasty (THA), we conducted a randomized controlled trial using either indomethacin or rofecoxib for 7 days.

**Methods** 186 patients received either indomethacin 3 times daily, or rofecoxib twice, and 1 placebo, daily for 7 days. HO was graded according to the 1-year postoperative radiographs according to the Brooker classification.

**Results** 12 of the 186 patients included discontinued their medication before the end of the trial due to side effects. The remaining 174 patients were included in the analysis. In the indomethacin group (n = 89), 77 patients (87%) showed no HO, 9 showed HO of grade 1 and 3 showed HO of grade 2 according to the Brooker classification. In the rofecoxib group (n = 85) 73 patients (86%) showed no ossification, 9 showed grade 1, and 3 showed grade 2.

**Interpretation** The prophylactic effect of rofecoxib for 7 days in preventing heterotopic ossification after primary total hip arthroplasty is comparable to the effect of indomethacin given for 7 days. These results indicate that the development of HO follows a COX-2 pathway.

Although indomethacin is effective in preventing heterotopic ossification (HO) after primary total hip arthroplasty (Kneller et al. 1997, Neal et al. 2000), side effects are frequently observed. The minimum treatment period for NSAIDs appears to be 7 days (Neal et al. 2000). Indomethacin used for 3 (van der Heide et al. 1999) or 4 (Dorn et al. 1998) days was found to show inferior results. Traditional non-steroidal anti-inflammatory drugs inhibit both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). In recent years, selective COX-2 inhibitors have been developed; these provide comparable pain reduction but with fewer side effects (Bombardier et al. 2000, Feldman and McMahon 2000, Silverstein et al. 2000) and reduced perioperative blood loss (Weber et al. 2003). Due to this reduction in side effects, these COX-2 inhibitors are attractive options for the prevention of heterotopic ossification.

To our knowledge, no data are available in the literature concerning whether the reduction of the heterotopic ossification after total hip arthroplasty in humans is a COX-1 or COX-2 effect, or the result of a yet unknown pathway. To investigate the incidence of heterotopic ossification (HO) after primary total hip arthroplasty (THA), we conducted a double-blind randomized controlled trial for prophylaxis using either indomethacin or rofecoxib for 7 days.

## Patients and methods

After approval by the local ethics committee, the study was initiated in Rijnstate Hospital, Arnhem, the Netherlands, which is a teaching hospital. The inclusion and exclusion criteria were as follows.

Inclusion criteria: primary hip arthroplasty, spinal or epidural anesthesia, able to sign an informed consent form, and age between 18 and 85 years. Exclusion criteria: previous surgery on the same hip joint, inclusion in another study, any history of bleeding disorders, any history of gastric ulcer, or rheumatoid arthritis.

All patients who were included signed a written informed consent. A power analysis was performed to calculate the number of patients needed for this study. From this calculation, we intended to include 200 patients. However, the inclusion of patients for this study was terminated on the day Merck withdrew rofecoxib from the market, i.e. September 30, 2004 (Couzin, 2004, Dieppe et al. 2004). At that time, 186 patients had already been included (58 males and 116 females). All non-steroidal anti-inflammatory drugs were stopped 10 days before surgery. Patients started their medication on the morning of surgery and continued it until the sixth postoperative day; thus, the trial period was 7 days. Each patient who was included received a package with 21 capsules, 7 labelled “morning”, 7 “afternoon”, and 7 “evening”. The medication was repacked in numbered packages, and the pharmacologist executed the randomization procedure. The packages were used under code by both patients and physicians. In the rofecoxib group, the patients received 3 capsules a day; the morning and evening tablet consisted of 25 mg rofecoxib, and the afternoon tablet was a placebo. In the indomethacin group, patients received indomethacin (50 mg) 3 times a day. No other NSAIDs were allowed for two months postoperatively. When necessary, patients were allowed to take acetaminophen (Paracetamol).

All hips were implanted using the posterolateral approach and all patients received 2 g cefazoline i.v. before surgery. A suction drain was used, which was removed on the first or second day postoperatively. All patients started weight bearing mobilization on the first postoperative day. Thrombo-embolic prophylaxis was given in a daily subcutaneous injection

The distribution of HO between the two treatment groups, no difference

Heterotopic ossification (Brooker grading)	Indomethacin (n = 89)	Rofecoxib (n = 85)
Grade 0	77 (87%)	73 (86%)
Grade 1	9 (10%)	9 (11%)
Grade 2	3 (3%)	3 (3%)
Grade 3	0	0
Grade 4	0	0

tion of 0.3 mL nadroparine (Fraxiparine) (2,850 IE) for 6 weeks.

All patients were reviewed 1 year postoperatively by one investigator (HvdH), and the pelvic radiographs were scored for HO according to Brooker et al. (1973). The investigator was blinded as to the prophylactic treatment given to the patient.

We used SPSS software version 11.5 for statistical analysis. The incidence of HO was estimated in both groups. Confidence intervals for these estimates were computed using the normal approximation to the binomial distribution, as was the confidence interval for their difference.

## Results

12 patients (7%) of the 186 patients who were included discontinued their medication before the end of the trial due to side effects, mainly nausea and vomiting (6 in the indomethacin group and 6 in the rofecoxib group), and they were excluded from further analysis. Of the 174 remaining patients, 86% of the patients in the rofecoxib-group (95% CI 78–93%) showed no signs of HO, as compared to 87% (95% CI 79–94%) in the indomethacin group (Table). This difference (1%, 95% CI –10 to 11%) was not significant ( $p = 0.9$ ).

## Discussion

We found no difference between the selective COX-2 inhibitor rofecoxib and indomethacin in the prevention of heterotopic ossification after primary THA. Considering the effectiveness of NSAIDs (Kneller et al. 1997, Neal et al. 2000) and the fact that in our hospitals all patients receive standard

NSAID prophylaxis for HO, from an ethical standpoint we elected not to use a placebo-controlled study design.

Although indomethacin is a powerful drug for prevention of heterotopic ossification, the high incidence of side effects (Neal et al. 2000) poses a clinical problem. Knelles et al. (1997) showed 22% side effects which resulted in study withdrawal of 2%. Cella et al. (1988) found contraindications to indomethacin in one-fifth of patients and one-third of their patients were withdrawn from the study.

Given the side effects of indomethacin, several other NSAIDs have been investigated for their prophylactic effect on HO. In recent years, more COX-2 selective inhibitors have been developed with fewer side effects (Bombardier et al. 2000, Feldman and McMahon 2000, Laine 2002, Gajraj 2003) and the same pain-reducing effects (Degner et al. 1998, Dequeker et al. 1998, Hawkey et al. 1998, Schoenfeld 1999, Feldman and McMahon 2000). The effect on HO of this newer class of NSAIDs is described circumstantially: the effect of meloxicam is contrasting; some studies have shown the same effect (Legenstein et al. 2003, van der Heide et al. 2004), while another showed inferior results (Barthel et al. 2002). The effect of celecoxib has been described by Romano et al. (2004), and is comparable to the effect of indomethacin. The latter authors found, however, that fewer patients in the celecoxib group had to discontinue their medication due to side effects as compared to those in the indomethacin group. In our study, the proportion of patients who stopped their medication before the seventh day was similar to these results (7%). In our study, it is striking that the number of patients who discontinued their medication due to side effects was exactly the same in both groups.

To our knowledge, there have been no publications reporting the effect of rofecoxib on HO after primary total hip replacement. The only paper addressing the possible effect of rofecoxib on HO was the study by Banovac et al. (2004). However, these authors described the prophylactic effect on HO after spinal cord injury. Although rofecoxib has been withdrawn from the market, we consider that the current study is still interesting because little is known about the effect of the selective COX-2 inhibitors on the incidence of HO. It is likely

that the prophylactic effect of rofecoxib is a class effect of all COX-2 selective inhibitors, and this study gives more information regarding the effect of this specific group. Furthermore, rofecoxib may perhaps be re-introduced onto the market for short-term use. Another important advantage of this new class of drugs may be the reduction of perioperative blood loss. Kristensen et al. (1990) found increased perioperative blood loss after the use of indomethacin, due to the reduction in platelet aggregation. Weber et al. (2003) found a decrease in perioperative and postoperative blood loss of 15% in the meloxicam group relative to the indomethacin group. However, serious concerns have been raised about the possible deleterious effects of NSAIDs—and especially the COX-2 selective ones—on bone healing and bone ingrowth in implants (Aspenberg 2002, 2005b, Burd et al. 2003, Dahners and Mullis 2004). Given the two additional risk factors, i.e. the increased cardiovascular risk after long-term use and the potential reduction in bone ingrowth in uncemented prostheses (Aspenberg 2005a, b), this class of drugs must also be fully investigated regarding these two issues before widespread use can be recommended.

In conclusion, the prophylactic effect of giving rofecoxib for seven days for prevention of heterotopic ossification after primary total hip arthroplasty is comparable to the effect of indomethacin given for 7 days.

#### *Note added in proof*

A similar study, which we were unaware of, is also published in this issue of *Acta Orthopaedica* (Grohs et al. 2007). The other study shows the same results as ours, but the incidence of HO was much higher in both treatment arms. This can be explained by the surgical (anterolateral) approach used in their study. A posterolateral approach was used in our study. It is known from the literature that the incidence of HO using an anterolateral approach is higher (Bischoff et al. 1994, Eggli and Woo 2001).

#### *Contributions of authors*

HvdH, WR, AvS, BS: study design and execution of the study. HvdH, WR, AvS, AvK, BS: analysis and interpretation of the data and preparation of the manuscript.

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